‘THE PREVALENCE OF OCCULT BLADDER DYSFUNCTION AMONG DIABETIC SUBJECTS ATTENDING AN ENDOCRINOLOGY OUTPATIENT CLINIC’

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A dissertation submitted to The Dr. M.G.R. Medical University, Tamilnadu, in partial fulfillment of the requirements for M.Ch. Branch-IV (Genitourinary surgery) examination to be held in August 2008.

CERTIFICATE

This is to certify that this dissertation entitled **"THE PREVALENCE OF OCCULT BLADDER DYSFUNCTION AMONG DIABETIC SUBJECTS ATTENDING AN ENDOCRINOLOGY OUTPATIENT CLINIC"** is bonafide work done by **Dr.Shanmugasundaram. R** in partial fulfillment of the rules and regulation for M.Ch. Br. IV (Genitourinary Surgery) examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be held in August 2008.

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ACKNOWLEDGEMENTS

I wish to express my deep gratitude to Dr. Ganesh Gopalakrishnan, M.S., M.Ch, F.R.C.P (Edin), F.A.M.S., Professor & Head, Dept. of Urology, Christian Medical College & Hospital, Vellore for his constant encouragement throughout the course of this study.

I am thankful to Dr. Nitin S Kekre, M.S, DNB (Urology), Professor, Dept. of Urology unit -II, Christian Medical College & Hospital, Vellore for his valuable guidance and kind help in the successful completion of the study.

I would like to thank Dr. Nihal Thomas, M.D, MNAMS (Endo). FRACP (Endo), Associate Professor, Department of Endocrinology, Christian Medical College & Hospital, Vellore for his guidance and encouragement.

I sincerely thank Dr. S. Sivan Arul selvan, M.D (Gen.Med), Dr. K. Felix Jebasingh, M.B,B.S, Dr.Suresh Prabhu, M.D (Gen.Med), Dr. George T Koshy, M.D (Gen.Med), Miss. Ruth Murray (Diabetic educator) for their kind co-operation in recruitment of patients for this study.

I also thank Mr. Solomon Christopher, M.Sc (Biostatistics), Department of Biostatistics, for his comprehensive statistical analysis.

I am thankful to all Urology department staff for their kind co-operation in doing necessary tests in the treatment room.

I would like to thank Medical records officers Mr. Nelson and Mr.Mohan for their help in recruitment of patients.

I express my deep gratitude and sincere thanks to all the diabetic patients who actively participated in this study and helped me to complete this study.

CONTENTS

INTRODUCTION

Diabetes is one of the most common chronic diseases affecting people world wide. The increasing prevalence of Diabetes all over the world is a major public health concern. The prevalence of diabetes in the adults will rise from 135 million in 1995 to 300 million by the year 2025, and more than 75% of the diabetics will reside in developing countries as compared to 62% in 1995. By 2025, India, China and the U.S will have the largest number of people with diabetics [1]. Several factors have contributed to the increasing burden of diabetes. These include a specific increase in risk factors for type 2 diabetes, such as increasing obesity [2, 3], lack of adequate physical activity [4], and life style and food changes induced by urbanization. Another factor contributing to apparent increase in the prevalence of diabetes has been the improvement in surveillance systems for diabetes, which has allowed better assessment of the true burden of diabetes [5]. Along with increased incidence of diabetes, complications caused by diabetes are also on the rise. Diabetes has its influence on multi-organ involvement in chronic diseases. Diabetes affects every organ due to macrovascular, microvascular and metabolic changes.

Diabetic cystopathy (DC) is a chronic known complication among diabetics with prevalence of 26% to 87% [6]. It has a significant impact on day-to-day life, predisposes individuals to urinary tract infections (UTIs), potentiates renal complications and compromises optimum health. It is characterized by impaired bladder sensations, increased bladder capacity, decreased detrusor contractility and increased residual urine. Diabetic cystopathy develops insidiously and

symptoms do not appear until the disease is well advanced. The classic symptoms of diabetic cystopathy which have been described have not always been observed in diabetic patients and these subjects often demonstrate variable symptom presentations. Initially the patient may be entirely asymptomatic, but demonstrate abnormalities on urodynamic study [7]. If bladder dysfunction is diagnosed earlier, corrective measures like strict glycemic control, changing the voiding pattern to timed voiding or double voiding may halt the deterioration of renal function, decrease the chance of urinary tract infection and halt progression of cystopathy further. Many authors have proposed that the diabetic cystopathy as a component of diabetic neuropathy which occurs in subjects with long standing diabetes. A weak association between glycemic control and neuropathic changes has been documented in both type 1 and type 2 diabetes. A possible link between deterioration of renal function and chronic asymptomatic bacteriuria in individuals with diabetes and bladder dysfunction also has been postulated [8, 9]. Lack of association between cystopathy and progression of diabetic nephropathy was shown in another study [10]. In this scenario, it is imperative for the treating physicians to diagnose bladder dysfunction in diabetics at an asymptomatic stage and institute early treatment for this condition to prevent or delay complications like recurrent urinary tract infection, urolithiasis, urinary incontinence and renal failure.

AIM OF THE STUDY

To estimate the prevalence and pattern of occult bladder dysfunction in diabetic subjects of 18 to 60 years age attending endocrinology outpatient clinic.

REVIEW OF LITERATURE

NEURAL CONTROL OF LOWER URINARY TRACT

The bladder performs two important functions. First, it stores the urine resulting from continuous excretory process of the kidneys into a more convenient, socially acceptable and adequate volume. Second, bladder empties the urine with synchronous activation of all the smooth muscle resulting in uniform pressure rise. The lower urinary tract receives innervations from three sources: sympathetic, parasympathetic and somatic nervous systems (Figure 1). The sympathetic system controls urine storage while the parasympathetic is responsible for bladder emptying. The somatic system which is under voluntary control is used in reinforcement of the external urethral sphincter and pelvic floor.

Parasympathetic supply

The pre-ganglionic parasympathetic fibres with cell bodies in the intermediolateral grey columns of the sacral segments of S2 to S4 run in the pelvic splanchnic nerves through the pelvic plexus. Autonomic ganglia are present not only within the nerve trunks and plexus, also on its more peripheral branches as they ramify on and within the bladder wall.

Sympathetic supply

Pre-ganglionic sympathetic fibres with cell bodies in the intermediolateral grey areas of the thoracic and lumbar segments T10 to L2 travel in the sympathetic chain and then via the lumbar splanchnic nerves to the superior hypogastric plexus. From there the right and left hypogastric nerves ramify with the pelvic plexus. Sympathetically mediated inhibition of the bladder depends not on

NEUROANATOMY OF LOWER URINARY TRACT

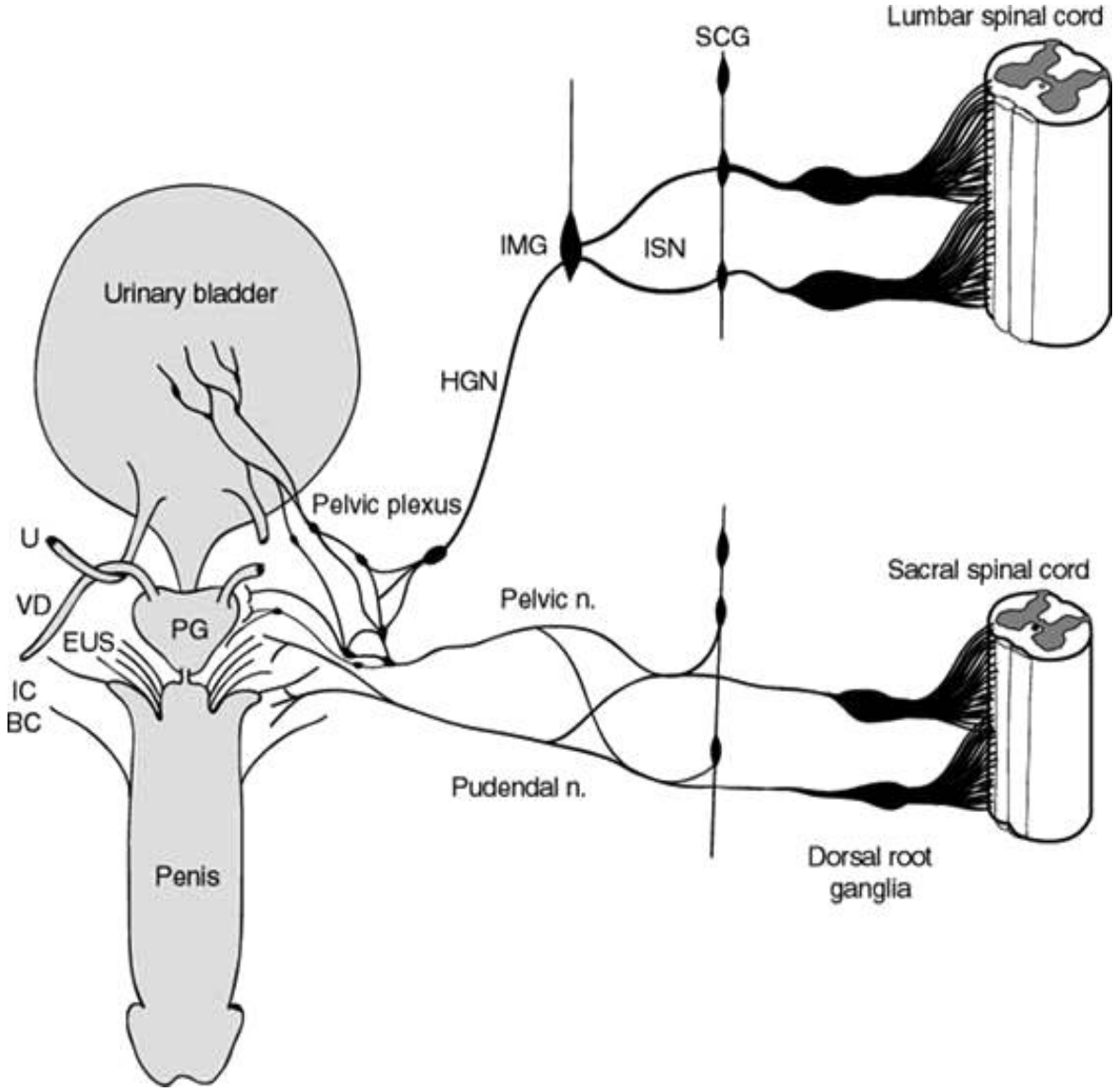

Figure 1. Innervation of lower urinary tract: Diagram showing the sympathetic, parasympathetic, and somatic innervation of the urogenital tract of male cat. Sympathetic preganglionic pathways emerge from the lumbar spinal cord and pass to the sympathetic chain ganglia (SCG) and then through the inferior splanchnic nerves (ISN) to the inferior mesenteric ganglia (IMG). Preganglionic and postganglionic sympathetic axons then travel in the hypogastric nerve (HGN) to the pelvic plexus and the urogenital organs. Parasympathetic preganglionic axons that originate in the sacral spinal cord pass in the pelvic nerve to ganglion cells in the pelvic plexus and to distal ganglia in the organs. Sacral somatic pathways are contained in the pudendal nerve, which provides an innervation to the penis, the ischiocavernosus (IC), bulbocavernosus (BC), and external urethral sphincter (EUS) muscles. The pudendal and pelvic nerves also receive postganglionic axons from the caudal sympathetic chain ganglia. These three sets of nerves contain afferent axons from the lumbosacral dorsal root ganglia. PG, prostate gland; U, ureter; VD, vas deferens.
(Adapted from Wein: Campbell-Walsh Urology, 9th ed. Physiology and Pharmacology of the Bladder and Urethra, p1937)

direct effects from noradrenergic fibres on the detrusor, but indirectly, by inhibition of the excitatory parasympathetic supply within the ganglia of the pelvic plexus. Noradrenaline released from the post-ganglionic sympathetic fibres, may be either excitatory or inhibitory depending on the predominant receptor type. Beta-receptors, producing relaxation have been shown to predominate in the vault of the bladder, while alpha-receptor sites producing contraction predominate in the bladder base.

Somatic nerve supply

The external urethral sphincter motoneurons are located along the lateral border of the ventral horn, commonly referred to as ***Onuf's nucleus*** [11]. Sphincter motoneurons also exhibit transverse dendritic projections into the lateral funiculus, intermediate gray matter and toward the central canal. Sacral somatic pathways are contained in the pudendal nerve, which provides an innervation to the external genitalia and perineal muscles. The pudendal and pelvic nerves also receive postganglionic axons from the caudal sympathetic chain ganglia.

Afferent Pathways

Visceral afferent fibres travel with both sacral and thoracolumbar visceral afferent nerves. Sacral afferents are evenly distributed between muscle and submucosa throughout the bladder; convey the sensations of touch, pain and bladder distension and are essential to complete normal micturition. Afferent axons in the pelvic, pudendal and hypogastric nerves transmit information from the lower urinary tract to the sacral and rostral lumbar dorsal root ganglia (DRG) which has their primary afferent neurons [12, 13]. The central axons of the DRG neurons carry the sensory information from the lower urinary tract to second-order neurons in

the spinal cord and visceral afferent fibers travel rostrocaudally within posterolateral (Lissauer's) tract. [9, 14, 15]. Pelvic nerve afferents consist of finely myelinated (Aδ) and unmyelinated (C) axons. These fibers are silent afferent and becomes mechanosensitive and unmasks new afferent pathway during inflammation (Table 1).

Table 1- Bladder afferent nerve fibers & their function

Fiber Type	***Location***	***Normal Function***	***Inflammation Effect***
Aδ (finely myelinated axons)	Smooth muscle	Sense bladder fullness (wall tension)	Increase discharge at lower pressure threshold
C fiber (unmyelinated axons)	Mucosa	Respond to stretch (bladder volume sensors)	Increase discharge at lower threshold
C fiber (unmyelinated axons)	Mucosa muscle	Nociception to overdistention	Sensitive to irritants
		Silent afferent	Becomes mechanosensitive and unmasks new afferent pathway during inflammation

Spinal and Supraspinal Pathways Involved in the Micturition Reflex

Spinal Cord

In the spinal cord, afferent pathways terminate on second-order interneurons that relay information to the brain or to other regions of the spinal cord including the preganglionic and motor nuclei. The axons of these second-order neurons cross

the midline and ascend in the anterolateral quadrant of the contralateral half of the spinal cord, where they join the spinothalamic tract. The second-order neurons ultimately synapse on neurons in the ventral posterior lateral nucleus (VPL) of the thalamus. Interneuronal mechanisms must play an essential role in the regulation of lower urinary tract function [16]. Glutamic acid is the excitatory and γ-aminobutyric acid (GABA) and glycine are the inhibitory transmitters in these pathways [17]. Reflex pathways that control the external sphincter muscles also use glutamatergic excitatory and GABAergic and glycinergic inhibitory interneuronal mechanisms. The micturition reflex can be modulated at the level of the spinal cord by interneuronal mechanisms activated by afferent input from cutaneous and striated muscle targets. Stimulation of afferent fibers from various regions (anus, colon-rectum, vagina, uterine cervix, penis, perineum, pudendal nerve) can inhibit the firing of sacral interneurons evoked by bladder distention [18]. Suppression of detrusor overactivity in patients by sacral root stimulation may reflect in part activation of the afferent limb of these visceral-bladder and somatic-bladder inhibitory reflexes [19].

Pontine Micturition Center (PMC)

Brainstem at the level of the inferior colliculus has an essential role in the control of the parasympathetic component of micturition [20]. The neurons in pontine micturition center (PMC) or the M region or Barrington nucleus send axon collaterals to the paraventricular thalamic nucleus (which is thought to be involved in the limbic system modulation of visceral behavior), periaqueductal gray region [21] (which regulates many visceral activities as well as pain

pathways) and to multiple supraspinal neuronal populations that may coordinate micturition with other functions of the organism. Neurons in the PMC provide direct facilitatory inputs to bladder outflow [22] and inhibitory influence on external urethral sphincter motoneurons [21]. As a result of these reciprocal connections, the PMC can promote bladder-sphincter synergy.

Central Pathways That Modulate the Micturition Reflex

The influence of the cortex on voiding function could be mediated by pathways including direct cortical projections from the prefrontal cortex and insular cortex to the PMC or projections through the hypothalamus and the extra pyramidal system. Lesions to these areas of cortex appear to directly increase bladder activity by removing cortical inhibitory control.

Applied anatomy

The neuropathic process in diabetes involves large myelinated, small finely myelinated Aδ and unmyelinated C fibers in the peripheral and central nervous system causing an array of neurological involvement with mixed pattern. It has been shown that spinal cord changes occurs in diabetes are similar to that of many demyelinating diseases like hereditary sensory motor neuropathy characterized by axonal atrophy and loss of anterior horn and dorsal root ganglion cells together with degeneration of the posterior columns in the spinal cord [23]. Bladder dysfunction is also considered as a manifestation of diabetic neuropathy. Hyperglycemia is proposed to lead to microvascular and neurologic complications, the neurologic sequelae ultimately resulting in a loss of myelinated

and unmyelinated fibers, wallerian degeneration, and blunted nerve fiber reproduction and function [24]. Involvement of afferent spinal and supraspinal tracts in diabetes may alter the pattern of inhibitory signals from central pathways to the sacral centers and predispose for detrusor overactivity as well as incontinence commonly seen in the clinical population with diabetic bladder dysfunction.

PHYSIOLOGY OF MICTURITION

Mechanisms governing the bladder to retain urine during the filling phase maintaining continence and expelling it when the desire void develops are a result of interplay between the autonomic and somatic nervous systems innervating bladder. The central pathways controlling lower urinary tract function are organized as simple on-off switching circuits that maintain a reciprocal relationship between the urinary bladder and the urethral outlet [25, 26]. Some reflexes promote urine storage, whereas others facilitate voiding. Individual reflexes are linked together in a serial manner to create complex feedback mechanisms. Alterations in these primitive reflex mechanisms may contribute to neurogenic bladder dysfunction. Direct activation of these reflexes by electrical stimulation of the sacral spinal roots very likely contributes to therapeutic effects of sacral nerve root neuromodulation [27].

Filling and storage phase

The bladder normally fills with urine at a rate of between 0.5 and 5 ml/minute and the bladder pressure rises only minimally. Even during the course of cystometry

at rapid filling rates the pressure rises by no more than 15 cm H2O from empty to cystometric capacity. This ability to adapt to an increase in volume is called the ***compliance.*** During the early stages of bladder filling, proprioceptive afferent impulses from stretch receptors within the bladder wall pass via the pelvic nerves to sacral dorsal roots S2 to S4. These impulses ascend in the cord via the lateral spinothalamic tracts and descending impulses from the subcortical micturition centres subconsciously inhibit a detrusor motor response. As the bladder volume increases, the sensation of bladder filling associated with the desire to micturate is first consciously appreciated, usually at between 200 and 300 ml. The inhibition of detrusor contraction is now cortically mediated, although the desire to void may be further suppressed to subconscious levels again. With further filling, impulses within the visceral afferent fibres accompanying the sympathetic efferents to thoracolumbar roots T10 to L2 ascend to the cerebral cortex and a further desire to void is appreciated. During this time, in addition to the cortical suppression of detrusor activity, there may by a voluntary pelvic floor contraction in an attempt to maintain urethral closure. When a suitable time and site for micturition is selected the process of voiding commences. This may be considered in two phases, the initiation phase and the micturition phase.

Initiation phase

Relaxation of the pelvic floor [28] occurs early in the process. Simultaneous relaxation of the intrinsic striated muscle also occurs. Descending inhibitory influences from the cerebral cortex acting on the sacral micturition centre are suppressed, allowing a rapid discharge of efferent parasympathetic impulses via

the pelvic nerves to cause detrusor contraction. As the force of detrusor contraction increases, residual urethral resistance decreases further. Urine flow commences when the falling urethral pressure and increasing intravesical pressure equate.

Micturition phase

Since the bladder at the initiation of micturition takes on a nearly spherical shape and has walls which are thin in comparison to its radius, its behavior may be expressed by the law of Laplace (P. 2T/R), where P. pressure, T. tension, and R. radius. As the mural tension rises in the absence of voiding the intravesical pressure also rises. When a critical opening pressure is achieved, urine will start to flow and the bladder radius will fall. The pressure, however, usually remains constant during voiding and thus the mural tension must fall. While active tension is required throughout, the effectiveness of detrusor contraction increases as the muscle fibres shorten and therefore decreasing forces are required as micturition proceeds. If micturition is voluntarily interrupted midstream, contraction of the pelvic floor (pubococcygeus) causes the urethral pressure to rise rapidly to exceed the intravesical pressure and therefore urine flow stops. The detrusor, being a smooth muscle, is much slower to relax and therefore goes on contracting against the closed sphincter. Thus an isometric contraction occurs and again, applying the law of Laplace, the intravesical pressure rises. If micturition is resumed by relaxation of the pelvic floor, both urethral and intravesical pressures will return to their previous voiding state.

Applied physiology

In diabetic cystopathy, due to neuronal damage afferent input resulting from the stretch of bladder muscle as well as the mucosa is affected. As bladder filling occur progressively, affected individual tend to accumulate large volume of urine. Frequency of micturition is often reduced during the later stages of the disease to the extent of voiding once or twice in a day. Bladder detrusor, like cardiac and skeletal muscle follow the principle to stretch as stated in starling's law of the heart [29]. As the detrusor stretches beyond the point where it can regain its tension, decompensation occurs. Detrusor can no longer expel urine in a single voiding. According to the law of Laplace, as the radius of distended bladder increases, mural tension decreases resulting in detrusor hypocontractility or acontractility. Studies also indicate that reduced production of nerve growth factor (NGF) in the bladder and/or impaired transport of NGF to L6–S1 DRG may be an important mechanism inducing DM cystopathy, which is attributable to defects in both Aδ fiber and C-fiber bladder afferent pathways [30]. NGF gene therapy using replication-defective HSV vectors which restore decreased NGF expression in the bladder afferent pathways could be effective for treating DM cystopathy [31].

EFFECTS OF DIABETES ON THE LOWER URINARY TRACT

Diabetes produces a spectrum of lower urinary tract manifestations with various symptoms. The bladder lesion due to diabetic neuropathy was first pointed out by Marchal de Calvi in 1864 [32]. Frimodt moller C coined the term “diabetic cystopathy” for the bladder symptoms occurring due to diabetes [6]. The classic triad of bladder symptoms associated with diabetic cystopathy includes decreased bladder sensation, increased bladder capacity, and impaired detrusor contractility with resultant increased postvoid residual (PVR) urine. Increased PVR leaves the individual prone to UTIs.

However, many diabetic patients have concomitant lesions, such as benign prostatic hyperplasia, stress incontinence, bladder or prostate cancer and infection, which may coexist with or mimic the symptoms of diabetic cystopathy. As a result, these patients complain of a variety of lower urinary tract symptoms that may obscure the underlying etiology. In addition, diabetes is a systemic disease whose prevalence as well as spectrum of symptomatic severity varies greatly depending on the population examined [33, 34]. Consequently, the classical symptoms of diabetic cystopathy (DC), while well described, have not always been observed in the diabetic patient and these patients often demonstrate varied symptom presentations. In a retrospective study of 182 diabetic patients who underwent videourodynamic evaluation [35], 55% had detrusor hyperreflexia, 23% had impaired detrusor contractility, 11% had indeterminate findings, 10% had detrusor areflexia and 1% was normal. Bladder outlet obstruction occurred in 66 patients (36%). The diagnosis was isolated in 24 patients (36%) or in

combination with another diagnosis in 42 (74%).This study indicated that classical diabetic cystopathy is not the most common urodynamic findings in patients with diabetes mellitus and voiding dysfunction, and in fact these patients present with variable pathophysiological findings.

An important question is whether bladder dysfunction is secondary to an inherent neuropathology induced by diabetes, or caused by changes associated with bladder over distension. Many animal models have been used to elucidate this and other questions seen in diabetic patients associated with diabetic cystopathy. Streptozotocin (STZ) induced diabetic rats and sucrose drinking rats have generally been used. Paro et al noted that alloxan induced diabetic rats had decreased and irregular contractions, while sucrose fed rats had normal bladder contractions [36]. This suggested that in alloxan induced diabetes; contractile dysfunction is secondary to an inherent diabetic cystopathy, while bladder hypertrophy in sucrose fed rats is an organ adaptation to polyuria. Neuropathy in diabetics has been extensively studied in recent years [37, 38] but none of these large trials included outcome measures relating to bladder dysfunction. Increasingly, DC is described as a manifestation of autonomic neuropathy [39, 40]. Although some believe it also represents peripheral somatic neuropathy [41]. Several classification systems for diabetic neuropathy have been suggested, but none has included specific lower urinary tract function. Greene et al [42] proposed that genitourinary neuropathy fits within the autonomic neuropathy category, along with sudomotor, cardiovascular, and gastrointestinal neuropathy as classified by Thomas et al [43] (Table 2).

Table 2 - Classification of diabetic neuropathy [43]

Diffuse
Distal symmetric sensorimotor polyneuropathy
Autonomic neuropathy:
Sudomotor
Cardiovascular
Gastrointestinal
Genitourinary
Symmetric proximal lower limb neuropathy (amyotrophy)
Focal
Cranial neuropathy
Radiculopathy / plexopathy
Entrapment neuropathy
Asymmetric proximal lower limb neuropathy (amyotrophy)

PATHOPHYSIOLOGY OF BLADDER DYSFUNCTION IN DIABETES

The biology of diabetes associated bladder complications is multifactorial and they can be a result of an alteration in the physiology of the detrusor smooth muscle cell, the innervation or function of the neuronal component, or urothelial dysfunction.

Diabetes and detrusor smooth muscle function:

DM has been shown to alter detrusor smooth muscle function in experimental STZ rat model. Pharmacological studies on isolated bladder muscle strips have shown varied responses. They are increase in responsiveness of detrusor muscle to externally applied muscarinic agonists [44, 45], increase in muscarinic receptor density [46], and an increase in the beta 1- receptor-mediated relaxation of isolated detrusor smooth muscle strips [47]. Other changes are increased responsiveness of isolated rat bladder strips to electrical field stimulation (EFS) [48, 49], increased neurotransmitter release, increased calcium-channel activity [50] and changes in nitric oxide synthase (NOS) and reactive nitrogen species formation [51].

Urothelial dysfunction in Diabetes:

Urothelium regulates permeability, transport and endocytosis. Urothelium is not only a passive barrier against urea and ion diffusion, but that it can also function as a sensor, controlling bladder function and dysfunction. The urothelium have receptors and ion channels similar to those in bladder nerves, and injury or inflammation may alter the response of both urothelial cells and sensory afferents to nociceptive and other stimuli. Many mediators, e.g. ATP, NO and prostanoids,

can be released from the urothelial cells [52, 53]. Vanilloid receptors are expressed on urothelial cells [54], and it has been shown that ATP can potentiate the response to vanilloids by lowering the threshold for, e.g. protons and capsaicin [55]. This means that the large amounts of ATP released from damaged/sensitized cells in response to injury/inflammation may influence afferent nerves and contribute to the variety of abnormalities in diabetes induced bladder dysfunction. In isolated urothelial layer preparations from bladders of STZ-Diabetic rats, the absolute amount of endogenous prostaglandins E2 and F2a was higher than in corresponding preparations from control animals [56]. ATP and bradykinin significantly increased the endogenous release of both prostaglandins from the urothelium. ATP and bradykinin receptors might be present in the urothelium and that these receptors may be important in, e.g. prostaglandin generation and release [57]. In turn, prostaglandins may sensitize sensory nerves and increase the sensitivity of bladder smooth muscle to contractile stimuli, which may contribute to some of the bladder abnormalities, e.g. detrusor overactivity, observed in diabetes.

Diabetic neuropathy causing bladder dysfunction:

The pathogenesis of diabetic neuropathy is multifactorial. Accumulating evidence suggests that the various pathogenic factors are interrelated and together contribute to the development and progression of the neuropathy [58, 59]. The actual process of neuropathic progression is dynamic (Figure 2), with nerve degeneration and regeneration occurring spontaneously and simultaneously. The

net balance between these two processes determines whether the neuropathy progresses, regresses or stabilizes.

Metabolic factors:

The results from the Diabetes Control and Complications Trial (DCCT) convincingly demonstrated that hyperglycemia and insulin deficiency contribute significantly to the development of diabetic neuropathy [37, 60]. Most of our understanding of pathogenetic mechanisms in diabetic neuropathy comes from studies in diabetic rats. One of the most often cited mechanism account for the effects of hyperglycemia on diabetic neuropathy is the changes in the polyol pathway. This leads to cell's inability to detoxify reactive oxygen species. Hyperglycemia also promotes formation of reactive oxygen species by auto-oxidation of glucose and formation of advanced glycation end products. In diabetic animals, accumulation of sorbitol in nerves in the presence of hyperglycemia produces a reciprocal decrease in levels of myo-inositol and taurine which are effective osmolytes [61]. Myo-inositol and taurine depletion is associated with reduced Na+/K+ adenosine triphosphatase activity resulting in Na+ retention, edema, myelin swelling, axoglial disjunction, nerve degeneration and slowed nerve conduction velocity in the diabetic rat [61, 62, 63]. Aldose reductase inhibitors restore myoinositol and taurine levels and improve motor conduction velocity in diabetic rats [57, 64]. They also improve nerve conduction velocities and protect small sensory fibers from degeneration in humans. In experimental diabetic neuropathy, antioxidant therapy has ameliorated signs of diabetic neuropathy [65].

Microvascular insufficiency:

Studies suggest that absolute or relative ischemia exists in the nerves of diabetic persons due to altered function of the endoneurial and/or epineurial blood vessels. Sural nerve biopsies from diabetic patients reveal many changes suggestive of endoneurial and epineurial microvasculopathy, including basement membrane thickening, endothelial cell proliferation, and vessel occlusions [66, 67]. Ischemia secondary to vascular disease induces oxidative stress in the nerve, increasing the production of reactive oxygen species and inducing nerve injury. Hyperglycemia- induced depletion of nicotinamide-adenine dinucleotide phosphate [NADPH] stores, with subsequent loss of detoxification mechanisms, further exacerbates the damage resulting from ischemic oxidative stress.

Growth factor deficiency:

Neurotrophic factors are involved in the development, maintenance, and regeneration of responsive elements of the nervous system. The best studied of these is nerve growth factor (NGF), a protein that promotes the survival of sympathetic and small-fiber neural crest-derived sensory neurons in the peripheral nervous system. These neurons are frequently affected in diabetic polyneuropathy. In diabetic animal models, both NGF production and retrograde transport appear to be impaired [68]. In a human study, abnormal expression of NGF in skin keratinocytes correlates with early manifestations of small fiber sensory neuropathy. Nerve growth factor treatment of streptozocin-diabetic rats and diabetic patients in clinical trials appears to ameliorate manifestations of small-fiber sensory neuropathy [69]. Neurotrophic factors appear to play a

significant role in mediating the cell's defense against oxidative stress. Deficiency in the availability of these factors could further exacerbate the injury caused by oxidative stress. Antioxidant treatment also enhances NGF action [70]. The insulin-like growth factors (IGFs), IGF-I and IGFII, have been implicated in the growth and differentiation of neurons and IGF receptors are present in nerve tissues (e.g., neurons, Schwann cells, ganglia) involved in diabetes- associated nerve disorders. IGFs and their binding proteins (IGF-BPs) are regulated by insulin and the glycemic state [71, 72]. A consequence of insulin insufficiency is a reduced circulating IGF-I concentration.

Immune mechanisms:

Immune mechanisms may be responsible for the clinical neuropathic syndrome, especially in those with proximal neuropathy and those with a more marked motor component to their neuropathy. Circulating antineuronal antibodies are present in diabetic serum in some patients. The circulating autoantibodies directed against motor and sensory nerve structures have been detected by indirect immunofluorescence, and antibody and complement deposits in various components of sural nerves have been shown. Anti-Gangliomucopolysaccharide (Anti-GM1) antibodies and Antiphospholipid antibodies (anti-PLAs) have been demonstrated in diabetic patients with neuropathy, especially distal symmetrical polyneuropathy (DSPN) [72, 73]. PLAs are associated with a tendency to vascular thrombosis; their presence may provide a link between the immune and vascular theories of causation of neuropathy.

Miscellaneous:

Other possible contributors to diabetic nerve damage include decreased expression of laminin, a glycoprotein important in nerve regeneration and Deficiency of dihomo-g-linolenic acid (GLA) as well as *N*-acetyl-L-carnitine. [71].

These mechanisms (Figure 2) appear to be working in unison to cause peripheral nerve degeneration in diabetic patients. Understanding these mechanisms provides opportunities for intervention. For example, aldose reductase inhibitors may offset the intracellular metabolic consequences of hyperglycemia, while antioxidants directly limit damage from reactive oxygen species. Neurotrophic factors, such as nerve growth factor, may also increase the resistance of the cell to injury from oxidative stress and at the same time promote regeneration of damaged nerves. All of these approaches are being investigated. Combination therapy may offer the greatest hope of ameliorating diabetic neuropathy (Figure 2). Tight control of blood glucose decreases long-term neurologic and microvascular complications of diabetes, but the precise relationship of glycemic control and duration of diabetes to diabetic cystopathy (DC) is not known. It even has been suggested that blood glucose concentration affects the rate at which aging occurs and that diabetes may be a syndrome of premature aging. [74].

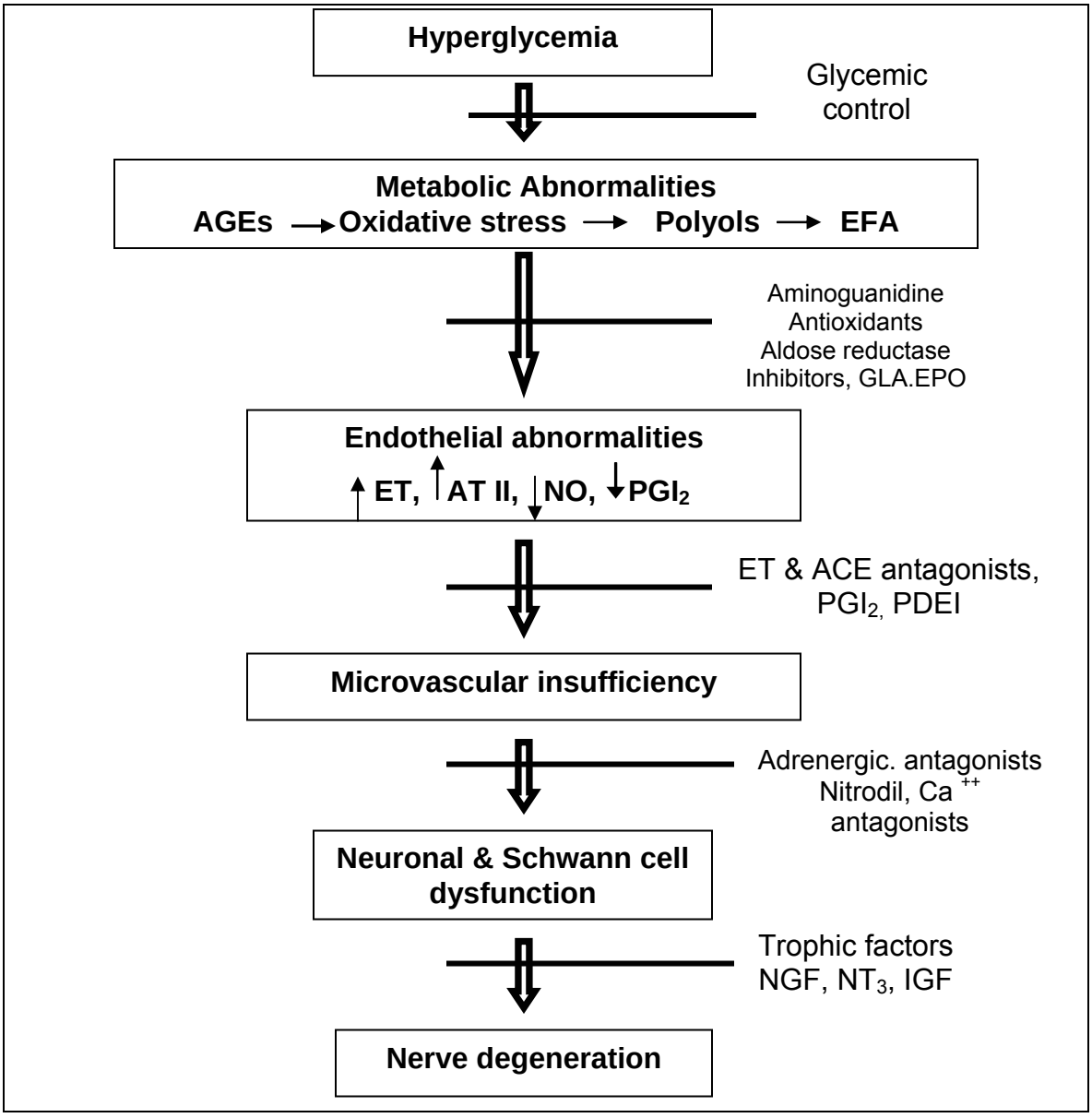

Figure 2: Steps in the proposed pathways that lead to the pathogenesis of diabetic neuropathy and possible interventions at the level of each proposed mechanism. [75]

AII = angiotensin II; ACE = angiotensin-converting enzyme; AGE = advanced glycation end products; EFA = essential fatty acid (deficiency); ET = endothelin; GLA/EPO = g-linolenic acid/evening primrose oil; IGF = insulin-like growth factor; NGF=nerve growth factor; Nitrodil=nitrodilators; NO=nitric oxide; NT3=neurotrophin-3; PDIE= phosphodiesterase; PGI2 = prostacyclin.

PREVALENCE OF BLADDER DYSFUNCTION IN DIABETES

Diabetic cystopathy develops insidiously and symptoms do not appear until the disease is well advanced [76]. The impact of disease duration and the method of treatment of diabetes on the development of diabetic cystopathy are not well established [35]. A large capacity bladder with concomitant retention and difficulty in voiding can occur in other diseases of non-diabetic origin [6]. Existing studies on diabetic cystopathy are generally characterized by a small number of cases that are selective either by studying subjects with diabetes of variable disease duration with urinary symptoms being referred for urologic examination or selecting a subgroup of patients with insulin dependent diabetes [76]. The prevalence of diabetic cystopathy in literature has been reported with different figures in various studies due to different definitions for cystopathy in them. Some investigators disregard the residual urine completely [6] and others accept over 90 to 1000ml of residual urine as diagnostic of cystopathy [7, 77, 78, 79]. Some others define cystopathy when residual urine volume exceeds 500ml to 1200ml [7] or when over 50% of bladder capacity has been reached [9, 80].

Frimodt-moller in urodynamic study of 124 diabetics (mainly insulin dependent diabetics), showed a prevalence of 38% of diabetic cystopathy [6]. Ellenberg & Weber [7] noted features of neurovesical involvement in 83% among 36 diabetic subjects with diabetic neuropathy when they compared the urodynamic and cystographic features of these subjects with normal 26 non-diabetic controls and 24 diabetic patients without neuropathy. They proposed the existence of preparalytic bladder with features of neurovesical involvement before the onset of

overt bladder dysfunction. Bartley et al had a prevalence of bladder dysfunction in 43% among 75 patients (28 men between 17 to 45 years old and 47 women of 17 -73 years old) with diabetes hospitalized for various reasons with combined urodynamic and cytographic studies [79]. Faerman et al noted a prevalence of 87% among 31 juvenile diabetics with average disease duration of 9 years using urodynamic and radiological techniques. Among those who had diabetes more than 10 years, 91% had bladder disturbances [9].

Fagerberg compared the cystometric, micturition urethrocystographic and pelvic floor electromyographic of 30 male hospitalized diabetics between 20 and 50 years of age with age matched control of 25 healthy male blood donors. The prevalence in this study was 34% to 65% [78]. In unselected diabetic patients on insulin, the frequency of cystopathy was 43-44% [80]. Urodynamic abnormalities suggestive of bladder dysfunction was noted in 80% among 60 diabetics (35 males and 25 females) by Buck et al. Electrophysiological testing in these patients revealed evidence of sensory defect in all of them [81]. The difference in the prevalence rates among all these studies may be due to1) lack of uniformity of definition of diabetic cystopathy 2) tools to diagnose bladder dysfunction and 3) patients factors like variable disease duration, glycemic control and associated complications such as sensory and motor neuropathy.

Kebapci et al evaluated 54 (27 men and 27 women) type 2 diabetic patients with LUTS using urodynamic studies and analyzed various parameters like disease duration, presence of diabetic autonomic neuropathy, nephropathy and retinopathy. 74% of the men and 59% of women had abnormal urodynamically

detected bladder dysfunction. 50% and 43.7% of men and women had features of diabetic cystopathy [82].

Various other Urodynamic abnormalities like bladder outflow obstruction and detrusor overactivity were also seen in significant number of patients. The diagnosis of diabetic cystopathy was established according to the following criteria: 1) Increased maximal bladder capacity 2) Impaired bladder sensation (volume at first desire to void >150ml) 3) decreased bladder contractility (a flat trace in cystometry) 4) post void residue of ≥ 100ml. Men with type 2 diabetes longer than 9 years and women with disease more than 8 – 9 years had higher risk of bladder dysfunction [82].

Ishigooka et al evaluated 42 patients with diabetes who were referred to urodynamic evaluation. A prevalence of 50% of diabetic cystopathy was seen. Urodynamic evaluations consist of water cystometry, uroflowmetry and measurement of post void residual urine. Diabetic cystopathy was diagnosed when patients had 1) impaired detrusor contraction (poorly sustained, no or weak detrusor contraction, (less than 30cmH2O or by uroflowmetry maximum flow rate less than 10ml/sec with or without staining voiding pattern) 2) Sensory impairment as defined as increased capacity at first desire to void (over ½ of maximum cystometric capacity) and / or maximum cystometric capacity over 600ml [83].

Many authors have demonstrated variable prevalence rate of bladder dysfunction among diabetics in various series using different methods of assessment. Majority of these studies were done in patients being referred for urologic

evaluation of their lower urinary tract symptoms or for other causes of hospitalization. There is paucity of studies describing the prevalence of bladder dysfunction among asymptomatic diabetic subjects who hasn't been evaluated for any urological symptoms. Upto our knowledge, there is no study in India which addresses this entity of bladder dysfunction in asymptomatic patients. The main purpose of this study is to know the prevalence of occult bladder dysfunction among diabetic patients.

ASSESSMENT OF BLADDER DYSFUNCTION IN DIABETES

As bladder dysfunction develops insidiously and often is detected when the clinical stage of the disease reaches an advanced stage, it was thought that urodynamic studies are mandatory for diagnosis of these conditions at the earlier stage [79]. In earlier series, bladder dysfunction was diagnosed when patients were referred for urodynamic evaluation in view of their lower urinary tract symptoms. Few studies have attempted to do estimate the prevalence of bladder dysfunction using non-invasive techniques like uroflowmetry and American urological Association (AUA) symptom index [84]. Uroflowmetry and post void residual urine of 182 diabetic female patients were compared with 197 normal healthy women [84]. Women with high AUA score index and lower maximum uroflow are noted to be likely parameters for bladder dysfunction. 25.8% of the women with type 2 diabetes in this study had bladder dysfunction. Lower maximum flow rate (<15ml/sec), Post void residual urine more than 100ml and Bladder voiding efficiency (BVE) {calculated as BVE = 100% X volume voided /

(volume voided + PVR)} less than 75% are defined as suggestive of bladder dysfunction in this study. In another study, an early disturbance of detrusor contraction noted by retarded uroflow in diabetic children and adolescents was interpreted as early sign of autonomic neuropathy. It has been suggested to use uroflowmetry to determine the autonomic neuropathy in them [85].

Estaghamati et al suggested the search for microvascular complications like neuropathy, retinopathy and nephropathy might be used to screen for components of diabetic cystopathy in its asymptomatic phase. 66 (26 males and 40 females) with low AUA symptom score were evaluated urodynamically along with assessment of microvascular complications. 29.2% of men had bladder outflow obstruction, 75% of women and 48% of men had increased bladder capacity, and 16.7% of patients had decreased compliance. Presence of somatic neuropathy on extremities suggested the low flow rate in the urodynamic study. Diabetic retinopathy had negative correlation with detrusor instability in this study. This study suggested the screening for diabetic cystopathy before the symptoms appear [86].

Prospectively voiding function of 176 diabetic women and 162 age matched nondiabetic women was assessed by AUA index questionnaire, uroflowmetry and post void residual urine estimation by urethral catheterization was done by Yu et al [87]. Maximum flow rate less than 12ml/sec at a minimum voided volume of atleast 150ml and post void residue more than 100ml was diagnostic of unrecognized voiding difficulty. Unrecognized voiding difficulty in diabetic women was 4.8 times more than in normal women. It was suggested that uroflowmetry

and AUA symptoms score might be used to identify those diabetic patients who are at risk of developing bladder dysfunction [87].

Although uroflowmetry and AUA symptom index are not specific to identify detrusor impairment, both these non-invasive parameters were suggested as tools to decide on the indication for further urodynamic investigations in diabetic patients [83, 84, 85]. In this study we used uroflowmetry and AUA symptom score to decide upon the further need for urodynamic in our study patients.

PATIENTS AND METHODS

Research Question:

1. What is the prevalence of occult bladder dysfunction among diabetic subjects between 18 to 60 years of age from Tamilnadu attending endocrinology-diabetic outpatient clinic?
2. What is the pattern of bladder dysfunction among the studied subjects?
3. Is there any association between the prevalence of bladder dysfunction between symptomatic and asymptomatic subjects?
4. Is there an association between bladder dysfunction and microvascular complications of diabetes?

Inclusion Criteria:

1. All Tamil speaking diabetic subjects between 18 to 60 years of age attending endocrinology – diabetic outpatient clinic.

Exclusion Criteria:

1. Previous surgery of urethra, prostate or bladder.
2. Previous pelvic procedures likely to cause bladder denervation like Hysterectomy and Abdominoperineal excision of rectum.
3. Neurological diseases likely to influence the lower urinary tract except autonomic neuropathy.
4. Overactive bladder, Bladder outlet obstruction or any other abnormal urodynamic findings.
5. Bladder calculus.
6. Bacterial and tuberculous cystitis

7. Medications like anticholinergics, diuretics, antidepressants and antipsychotics.

Calculation of sample size:

The sample size was calculated from a retrospective study analyzing the prevalence of bladder dysfunction among symptomatic diabetic patients who were referred and urodynamically evaluated in the department of urology for a period of three years. The prevalence of diabetic cystopathy was 40%. The sample size required to find a prevalence of 40% with a precision of ± 10% and with a 95% confidence was 100. Sample size was calculated using the formula: $4pq / d^2$, where p is 40%, q = 1-p = 60%, d = 10%. The primary endpoint was to estimate the prevalence of occult bladder dysfunction.

Methodology:

The study was conducted in the endocrinology- diabetic outpatient clinic and urology department of Christian medical college, Vellore. This was prospective cohort study. Diabetic subjects of age group of 18 to 60 years attending the endocrinology outpatient clinic were recruited for the study. Those who fulfill the inclusion and exclusion criteria were subjected for the study after written informed consent. They were asked to answer an international prostatic symptom score (IPSS) questionnaire (annexure 1). All subjects did a representative uroflowmetry. Post void residual urine was measured using abdominal ultrasound using prolate ellipsoid formula; Volume (V) in ml = Length x Height x transverse diameter x π/6 or 0.53. All maintained a bladder diary for 24 hours in their homes and returned the form during next visit. Those who have moderate lower

urinary tract symptoms (LUTS) as indicated by (IPSS score ≥ 8) or have a peak flow of less than 15ml/sec at a voided volume more than 150ml were subjected for urodynamic evaluation. All the demographic and clinical data were recorded in the proforma (annexure 2). Evaluation of patients began with detailed history of duration of diabetes, duration of LUTS, nature of LUTS, presence of incontinence / hematuria / calculuria/ necroturia / urinary tract infection / voiding dysfunction/ instrumentation, symptoms of cardiac/ peripheral vascular / neurological diseases. Physical examination details as recorded by diabetologist (co-investigator) were also entered. Urological clinical assessment was done by the investigator. Evaluation for concomitant diabetic neuropathy, nephropathy and retinopathy was carried out in all patients. Estimation of serum creatinine, Fasting and 2-hours post prandial glucose, HbA1C, Fasting lipid profile, Microalbumin or 24-hour urinary proteins and urine microscopy was done for all. Urine culture and sensitivity was done for those who were subjected to urodynamics. Ultrasonogram of the abdomen and X-ray of the KUB region was done for those who had other abdominal symptoms, microhematuria and renal failure. Those who have asymptomatic bacteriuria were included in the study. Those who have positive culture with LUTS were excluded from the study. The pressure-flow studies were done using medical measurement systems (MMS) UD 2000 equipment. Gentamicin Sulphate 160mg and Cefotaxime 1g was given intravenously as prophylactic antibiotics for those who had normal renal function and those with renal failure respectively. No antibiotic prophylaxis was given after urodynamic study. Pretest residue was measured prior to urodynamic evaluation

by placing two 6Fr infant feeding tubes. One of these tubes was used for filling as well as for intravesical pressure measurement. During cystometry in sitting posture, bladder was filled with physiological saline at 37ºC at a filling rate of 50ml/min. First sensation of bladder filling (ml), maximum cystometric capacity (ml), detrusor overactivity (presence or absence), incontinence (presence or absence), and compliance (cmH2O) were assessed during filling phase. Maximum urinary flow (Qmax, ml/sec), Maximum intravesical pressure on voiding (cmH2O), Voided volume (ml), events like abdominal straining were noted during voiding phase. Abdominal pressure was recorded by using perforated rectal balloon catheter. Detrusor pressure was calculated by subtracting intra-abdominal pressure from intravesical pressure. Detrusor pressure at maximum urinary flow rate (Pdet at Qmax, cm H2O) was measured to evaluate detrusor contractility. Methods, definitions and units were appropriate to the standards recommended by the international continence society. In those who did not undergo urodynamics, uroflowmetry, estimation of residual urine, bladder voiding efficiency (BVE) were the parameters evaluated to study bladder dysfunction. BVE was calculated by BVE= 100% x volume voided / (volume voided+ post void residue). BVE less than 75% was chosen as the cutoff point of bladder dysfunction.

Definition:

1) **Urinary incontinence** was defined if the complaint of any involuntary leakage of urine was present in which stress urinary incontinence (the complaint of involuntary leakage on effort on exertion, or on sneezing or coughing), or urge urinary incontinence (the complaint of involuntary leakage accompanied by or immediately preceded by urgency) were noted.
2) **Normosensitive bladder** - Volume at first sensation of 150 -200ml
3) **Delayed first sensation –** Appreciation of first sensation of filling at volume ≥250ml or greater than 50% of maximal cystometric capacity.
4) **Detrusor overactivity –** Involuntary phasic increase in detrusor pressure that was difficult to control or could not be controlled by patient resulting in incontinence or voiding.
5) **Normal compliance –** Filling detrusor pressure of 5-20cmH2O in the absence of simultaneous detrusor contraction at maximum cystometric capacity.
6) **Normal maximum cystometric capacity –** Volume 350 to 600ml, at which there was bladder contraction that resulted in voiding or patient discomfort.
7) **Normal urinary flow rate –** Catheterized urine flow rate of more than 12ml/sec.
8) **Normal Pdet at Qmax** - > 10cm H2O or <40cmH2O during voiding with catheterized flow rate if more than 12ml/sec.
9) **Normal post void residue** – 50ml

10) **Hypocontractile detrusor** – Pdet at Qmax less than 10cmH2O or flat trace during voiding with or without abdominal straining.

11) **Bladder outflow obstruction** – Pdet at Qmax more than 40cmH2O with catheterized urine flow rate less than 12ml/sec.

12) **Bladder dysfunction (among those who had urodynamics):** Presence of 2 or more of the following findings

   a. First sensation of filling at volume more than 250ml or 50% of maximum cystometric capacity
   b. Maximum cystometric capacity more than 600ml
   c. Compliance >20cmH2O
   d. Detrusor overactivity
   e. Pdet at Qmax <10 / >40cmH2O with catheterized flow rate less than 12ml/sec
   f. Post void residue more than 50ml.

13) **Bladder dysfunction (among those who did not have urodynamics):** Presence of 2 or more of the following findings

   a. Voided volume more than 600ml or less than 150ml
   b. Post void residue more than 50ml
   c. Bladder voiding efficiency less than 75%

14) **Diabetic nephropathy**

   a. Microalbuminuria: ≥30mg/day
   b. Macroalbuminuria: >300mg/day

15) **Diabetic retinopathy**

- ***a.*** Presence of background, nonproliferative or proliferative retinopathy
- ***b.*** History of laser retinal photocoagulation / vitreoretinal surgery in the course of diabetes

16) **Diabetic neuropathy**: Presence of more than 2 of the following elements

- ***a.*** Biothesiometry >20mv
- ***b.*** Monofilament >4g
- ***c.*** Deep tendon reflexes - absent or decreased
- ***d.*** Trophic ulcers

17) **Overt Diabetic cystopathy:** Presence of 3 or more of the following elements

a. First sensation of bladder filling at >250ml or 50% of maximum cystometric capacity
b. Maximum cystometric capacity >600ml
c. Pdet at Qmax <10cmH2O at a catheterized urine flow rate of 12ml/sec
d. Post void residual urine > 50ml

Analysis

All statistical analyses were performed using Statistical Package for the social Sciences (SPSS 11.0) for windows. Categorical data was presented using frequencies and percentage. Continuous data was described using mean ± standard deviation or median and range. Associations between categorical variables were assessed using chi-square test with yates' correction or fisher's exact test. Continuous variables were compared using student't' tests and Mann-Whitney tests were used for non-normal data. A p-value less than 0.05 was considered statistically significant.

RESULTS

Patients included in final analysis

A total of 90 patients were recruited for the study. Of 90 patients, 65 (72.2%) were males and 25 (27.8%) were females.

Prevalence of bladder dysfunction

Of 90 patients, 45 had urodynamic study according to the inclusion criteria and 45 others did not have urodynamic evaluation (non-urodynamics group). Over all 37 patients (41.1%) had bladder dysfunction and 53 patients (58.9%) did not have bladder dysfunction. In the urodynamic group, 35 of 45 (77.8%) had bladder dysfunction as defined in the study. In the non-urodynamics group, only 2 of 45 patients (4.4%) had bladder dysfunction. Age of the patients ranged from 20 to 58 years (mean age ± SD - 45.6 ± 8.12 years). Male patients were slightly older than females (46.23 ± 8.0 years in males against 44.2 ± 8.1 years in females). One half of the males and one fourth of the females had bladder dysfunction (P= 0.012) (table 3).

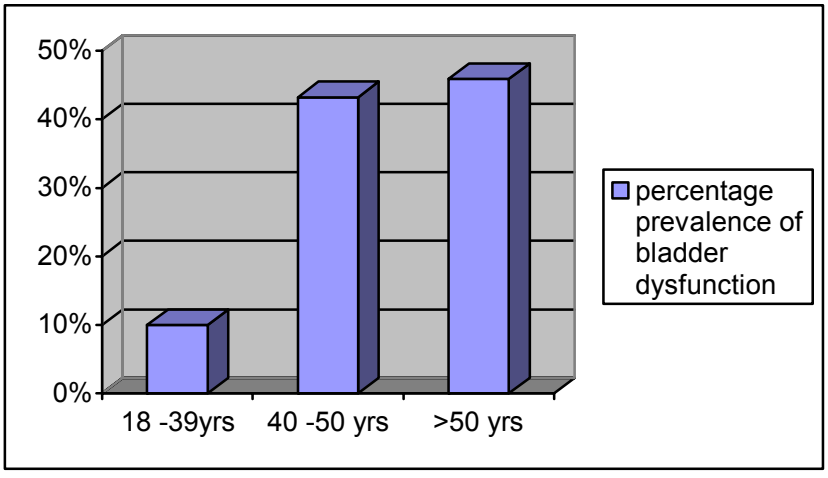

Figure 3: Prevalence of bladder dysfunction according to age group.

Patients were categorized according to the age into three groups namely: 1) 18 to 39 yrs (21.1%) 2) 40-50 yrs (48.9%) and 3) >50yrs (30%) (Figure 3). Bladder

dysfunction was seen more often in subjects with age >50 years (45.9%) (P = 0.012). A few patients (7/90) were type 1 diabetics and majority (83/90) were type 2 diabetics. Bladder dysfunction was seen often in type 2 diabetics, however it was not statistically significant (P =0.610). Mean duration of diabetes was 6.7 years (range 1-25). Bladder dysfunction was seen in subjects with longer duration of diabetes (6 years Vs 3 years) P= 0.042.

Table 3: Comparison of demographic features in bladder dysfunction

Variable	***Bladder dysfunction***		***P value***
	Yes	**No**	
Age (years) †	49.0 ± 8.9	43.3 ± 8.6	0.001 **
Males§	32 (49.2%)	33 (50.8%)	0.012 *
Females§	5 (20%)	20 (80%)	
Type I Diabetes§	3 (42.9%)	4 (57.1%)	0.610
Type II Diabetes§	34 (41%)	49 (59%)	
Duration of diabetes (years) ‡	6 (1 -25)	3 (1 -25)	0.042*

† - mean ± standard deviation
‡ - median (range)
§ - percentage
* - significant
** - Highly significant

Bladder dysfunction was seen 10 (18.9%), 24(70.6%) and 3(100%) in those who have mild, moderate and severe LUTS by IPSS (P <0.001) as denoted in table 4. There was no correlation between IPSS and the severity of bladder dysfunction. Bladder dysfunction was seen more often in those who complained of LUTS during questioning (P= 0.05).

Table 4: Comparison of Frequency –Volume chart (bladder diary), uroflowmetry & Bladder voiding efficiency in bladder dysfunction

Variable		***Bladder dysfunction***		***P value***
		Yes	**No**	
IPSS §	Mild	10 (18.9%)	43 (81.1%)	<0.001**
	Moderate	24 (70.6%)	10 (29.4%)	
	Severe	3 (100%)	0	
LUTS §	Absence	12 (30%)	28(70%)	0.05*
	Presence	25 (50%)	25(50%)	
Duration of LUTS (months)‡		6 (0-24)	0 (0-36)	0.002 **
Day time frequency (times)‡		7 (5-12)	6 (4-16)	0.264
Night time frequency (times)‡		2 (0-6)	1 (0-5)	0.007*
24-hrs Fluid intake(ml) †		2750 ± 1151	2712 ± 964	0.870
24-hrs urine volume (ml)†		2858 ± 1337	2386 ± 708	0.05*
Maximum bladder volume(ml) (bladder diary) †		582. 30 ± 218	502 ± 196	0.079
Qmax §	<15ml/sec	35 (77.7%)	10 (22.2%)	<0.001**
	>15ml/sec	2 (4.4%)	43 (95.6%)	
Voided volume	(>600ml)	19 (52.8%)	17 (47.2%)	0.05*
During uroflow §	(<600ml)	18 (33.3%)	36 (66.7%)	
Post void residue §	>50ml	14 (70%)	6 (30%)	0.003*
	<50ml	23 (32.9%)	47 (67.1%)	
Post void residue (ml) †		175.9 ± 232.4	52.4 ± 58.6	0.007*
Bladder voiding efficiency (%) †		87.7 ± 17.3	94.56 ± 5.13	0.025*

† - mean ± standard deviation

‡ - median (range)

§ - percentage

* - significant ** - Highly significant

Bladder dysfunction was seen in those who had LUTS for 6 months or more (P=0.002). Bladder dysfunction was seen more often in those who had nocturnal frequency (P=0.007). Diabetics with bladder dysfunction has slightly increased intake of fluid, but the difference between the groups was not significant (P=0.870). However there was significant difference between the group with bladder dysfunction and the group that did not have dysfunction in 24-hr urine output. It could be attributed to hyperosmolar state in poorly controlled diabetes, as evident by the increase in mean HbA1C level (8.46±2.03%) in those with bladder dysfunction. However it was not statistically significant from HbA1C levels seen in group which did not have bladder dysfunction. The mean 24-hr urine output in subjects with bladder dysfunction was 2858 ± 13ml and it was 2386 ± 70ml in those who did not have dysfunction(P=0.05).

There was a significant difference between subjects with bladder dysfunction and Those who did not have bladder dysfunction, when their peak urine flow was less than 15ml/sec (P=<0.001), voided volume was more than 600ml (P= 0.05) and post void residue was more than 50ml (P= 0.003). When the post void residual urine values was individually computed for both groups, patients with bladder dysfunction had significantly different high mean volumes as compared to those who did not have bladder dysfunction (175.9 ±232.4ml Vs 52.4 ± 58.6ml) (P =0.007). Mean bladder voiding efficiency was also significantly lesser in dysfunction group than in the group that did not have bladder dysfunction (87.7 ± 17% Vs 94.56 ± 5.13%) (P=0.025).

Prevalence of various urodynamic abnormalities in dysfunction group

The prevalence of various urodynamic abnormalities in detrusor activity, first sensation, maximum cystometric capacity, bladder compliance, bladder outflow obstruction (Pdet at Qmax of ≥40cmH2O + catheterized urine flow rate of 12ml/sec), hypocontractile detrusor (Pdet at Qmax <10cmH2O) and increased post void residue (>50ml) among those who had bladder dysfunction in the urodynamic group is shown in table 5. Increased maximum cystometric capacity was the commonest abnormality seen.

Table 6. Prevalence of various urodynamic abnormalities

Urodynamic abnormalities	**Prevalence – No (%)**
Detrusor overactivity	14 (31.1)
Increased maximum cystometric capacity	30 (66.6)
Decreased bladder compliance	15 (33.3)
Delayed first sensation	15 (33.3)
Bladder outflow obstruction	15(33.3)
Increased post void residue	25 (55.6)

Comparison of urodynamic parameters in bladder dysfunction

Delayed onset of first sensation of filling (>250ml or 50% of maximum cystometric capacity), increased maximum cystometric capacity (>600ml), peak catheterized flow rate ($Qmax^{Uro}$), post void residual urine (>50ml) and abnormal detrusor contraction (Pdet Qmax < 10 or > 40 cmH2O) were significantly different

between those who had bladder dysfunction and those who did not have dysfunction. However detrusor overactivity, compliance, detrusor pressure at peak catheterized flow rate (Pdet at Qmax ^{Uro}) was not significantly different between the two groups as denoted in table 7.

Table 7– Significance of urodynamic parameters in bladder dysfunction

Variable		***Bladder dysfunction***		***P value***
		Yes	**No**	
First sensation §	>250ml	15 (100%)	0	0.009*
	<250ml	20 (66.7%)	10 (33.3%)	
First sensation (of cystometric capacity) §	>50 %	31	53	0.004*
	<50%	6	0	
Detrusor overactivity		13 (92.9%)	1(7.1%)	0.102
Maximum cystometric capacity §	(>600ml)	19 (52.8%)	17 (47.8%)	0.05*
	(<600ml)	18 (33.3%)	36 (66.7%)	
Compliance §	>20cmH2O	14 (93.3%)	1 (6.7%)	0.077
	<20cmH2O	21 (70%)	9 (30%)	
Qmax ^{Uro} (ml/sec) †		10.7 ± 4.3	14.4 ± 3.6	0.016 *
Pdet at Qmax ^{Uro}(cm H2O) †		41.4 ± 21.5	32.4 ± 15.8	0.401
Pdet Qmax < 10 or > 40 §		23 (88.5%)	3 (11.5%)	0.05*
Post void residue (ml) †		175.9± 232.49	52.4 ± 58.6	0.007 *

† - mean ± standard deviation
‡ - median (range)
§ - percentage
* - significant ** - Highly significant

Comparison of clinical parameters in bladder dysfunction

Among the clinical parameters studied, presence of peripheral neuropathy was the only parameter found to be significantly different between the bladder dysfunction group and the group that did not have bladder dysfunction (P=0.018) (table 8). Presence of retinopathy, nephropathy, blood pressure values, body mass index (BMI) and associated diseases were not significantly different between the two groups. When biothesiometry and monofilament assessment was correlated individually with presence or absence of bladder dysfunction, only abnormal monofilament values were significantly different between the bladder dysfunction and the group without bladder dysfunction (P=0.022).

Table 8: Comparison of clinical parameters in bladder dysfunction

Variable	***Bladder dysfunction***		***P value***
	Yes	**No**	
BMI (kg/m²) †	24.6 ± 4.6	24.7 ± 4.3	0.160
Systolic blood pressure (mmHg) †	128 ± 19.9	126.6± 11.6	0. 588
Diastolic blood pressure (mmHg) †	80.16 ± 7.8	79.13 ± 6.4	0.535
Biothesiometry (>20mv) §	13(54.2%)	11(45.8%)	0.129
Monofilament (>4g) §	16(59.3%)	11(40.7%)	0.022*
Peripheral neuropathy §	18 (58.1%)	13(41.9%)	0.018*
Retinopathy §	15(50%)	15(50%)	0.226
Nephropathy §	2 (50%)	2 (50%)	0.546
Hypertension §	16(51.6%)	15(48.4%)	0.142
Dyslipidemia §	8(30.8%)	18(69.2%)	0.204
Ischemic heart disease §	5 (55.6%)	4(44.4)	0.281
COPD §	2(66.7%)	1(33.3%)	0.367
Hypothyroidism §	0	1(100%)	0.589

† - mean ± standard deviation,
§ - percentage, * - significant

Comparison of biochemical parameters with bladder dysfunction

Similarly there was no difference between the two groups in blood sugar levels, HbA1C, Microalbumin and lipid profile (table 9). Serum creatinine was the only biochemical parameter found to be significantly different between the bladder dysfunction group and the group which did not have bladder dysfunction. Only two of the patients with bladder dysfunction had clinical renal failure.

Table 9: Comparison of biochemical parameters with bladder dysfunction

Variable	***Bladder dysfunction***		***P value***
	Yes	**No**	
AC (mg %) †	140 ± 49	145 ± 45	0.678
PC (mg %) †	224 ± 78	214 ± 76	0.620
Serum creatinine (mg %) †	0.97 ± 0.24	0.86 ± 0.14	0.018*
HbA1C (%) †	8.46 ± 2.03	8.43 ± 1.85	0.420
Microalbumin (mg) †	69.05 ± 88.46	46.6 ± 79.15	0.312
Cholesterol (mg%) †	178.14± 42.36	182.15± 44.37	0.914
Triglycerides (mg%) †	162. 27 ± 69.34	153.45 ± 78.18	0.360
HDL (mg%) †	34.6± 6.18	36.94 ± 6.5	0.611
LDL (mg%) †	114.05 ± 32.83	120.06 ± 37.27	0.509

† - mean ± standard deviation

* - significant

DISCUSSION

In the previous studies, according to the diagnostic methods, criteria and patient characteristics, the frequency of diabetic cystopathy varies from 26% to 87% [6, 7, 9, 79]. The varied frequency of diabetic bladder dysfunction reported in the literature is due to varied definitions adopted and different combinations of investigations used by the authors. Frimodt-Moller et al first reported detailed clinical characteristics of bladder dysfunction in unselected diabetic patients. They characterized diabetic cystopathy as loss of sensation detected by elevated electrical bladder perception threshold which was found in 38% of patients [80]. According to the criteria proposed by Kahan et al [77], which defined diabetic cystopathy as an increase in bladder capacity to more than 400ml with flat trace on cystometry, 36% of diabetic subjects had diabetic cystopathy. Ueda et al [39] reported that 32% of diabetic patients had diabetic cystopathy using the criterion that bladder capacity exceeding 500ml was abnormal. In our study, with criteria for overt diabetic cystopathy which included maximum cystometric capacity (>600ml), Pdet at Qmax <10cmH2O at catheterized flow rate of less than 12ml/sec and impaired first sensation (>250ml or 50% of cystometric capacity) and PVR ≥50ml, overt diabetic cystopathy was found in 7/45 (15.5%) patients. When all the criteria for bladder dysfunction were applied, Overall prevalence of it was noted in 41.1% of the patients.

Kebapci et all has shown that IPSS was not different between those who have bladder dysfunction and those who did not have bladder dysfunction in their study of 54 type 2 diabetic patients. It was also not different among those who

had diabetic cystopathy and those who had other bladder dysfunction [82]. In our study mean IPSS was significantly different among the bladder dysfunction (9.7 ± 6) and non dysfunction group (4.3 ± 3.3) (P<0.001). However we could not establish a correlation between the IPSS and severity of bladder dysfunction. There was highly significant difference in peakflow among the bladder dysfunction group (17.13ml/sec) and group without bladder dysfunction (25.02 ± 8.32ml/sec) (P<0.001). The same difference noted for post void residue>50ml between these groups (70% Vs 50%) (P= 0.003). Thus its should be possible to predict the chances of bladder dysfunction in diabetics with basic tools of evaluation of lower urinary tract like uroflowmetry, estimation of post void residue and IPSS (peak flow less than 17ml/sec, IPSS >10 and PVR >50ml). However the sample size should be larger, to get more significant and consistent prediction of bladder dysfunction.

A number of clinical studies have reported detrusor overactivity as the most frequent finding, ranging from 39% to 61% of diabetic patients [88]. Detrusor overactivity can be due to bladder outflow obstruction or neurologic disease and moreover, it is common among elderly incontinent subjects [39]. Incontinence due to detrusor overactivity among women in the general population increases with age, starting at a prevalence / incidence of 20–30% in young-adult life (<40 years), rising to 30–40% in middle age (40–60 years), and 30–50% in the elderly (>60 years) [88, 89]. Similarly detrusor overactivity is also of high prevalence among elderly men with prostatic enlargement [90]. Men with diabetes have an increased risk of developing LUTS, reported to be 25–100% higher than in the

general male population [91]. In our study, in the absence of neurological disease other than diabetic neuropathy, among patients of bladder dysfunction, detrusor overactivity was seen in 13 patients (females -4, males -9) with prevalence of 29%. Of them, isolated detrusor overactivity, detrusor overactivity associated with BOO and associated with cystopathy was seen in 38.5%, 38.5% and 23% of patients respectively. Among females with detrusor overactivity, it was seen as an isolated abnormality in two and was associated with cystopathy in others. Among males with detrusor overactivity, it was seen isolated in 3, associated with BOO in 5 and associated with cystopathy in one. Mean age of males with detrusor overactivity was 51.4 years. Mean age of females with detrusor overactivity was 47.7 years.

Within the male population the most important differential diagnosis, and the one that frequently coexists with diabetic cystopathy is BOO [92]. Kaplan et al found that bladder outflow obstruction was seen in 66 men (prevalence of 36%) among their 182 patients who were evaluated with urodynamics [35].

Bladder outflow obstruction was seen 15 (33.3%) patients in our study. All except one were men. A 55 years old postmenopausal lady had BOO. The mean age of all men was them 47.2 years (range 39 – 58 years). 3 patients with BOO also had features of diabetic cystopathy. 5 had associated detrusor overactivity.

The patients who had bladder dysfunction had significant difference in maximum bladder volume as recorded in the bladder diary and higher 24-hr urinary volume (urine output). This could also be useful to predict bladder dysfunction provided the hyperosmolar state due to poorly controlled diabetes is ruled out. In our study

both the bladder dysfunction and non-dysfunction groups had raised HbA1C levels indicating inadequate glycemic control. This could be the reason for larger urinary volumes seen among subjects with bladder dysfunction. Kepabci et al have shown in their study that higher HbA1C levels were associated with higher prevalence of bladder dysfunction even though it was not statistically significant. There is well established correlation between bladder dysfunction and diabetic neuropathy [93]. The presence of abnormalities on neurological examination has been shown to predict bladder dysfunction. More than 85% of patients with positive sacral cord signs had abnormalities of detrusor contractions in one study [35]. In another study on 29 diabetic patients, 38 of whom had voiding dysfunction as defined by the presence of an abnormality in either flow rate, flow pattern, or post void residue, voiding dysfunction was strongly correlated with presence of neuropathy ($P<0.001$) [41]. Overall, a correlation ranging from 75% to 100% have been reported in previous studies [76]. In our study, 18 of the 31 (58.1%) patients with clinical evidence of peripheral neuropathy in lower limbs had bladder dysfunction, whereas only 19 of the 59 patients without neuropathy had bladder dysfunction ($P=0.018$). Presence of overt peripheral neuropathy could be used to predict the bladder dysfunction.

Esteghamati et al showed an inverse correlation between retinopathy and detrusor instability in an urodynamic study done in asymptomatic diabetic subjects [86]. About half the patients with diabetic cystopathy showed signs of retinopathy in study of 124 diabetic subjects [80]. In our study, prevalence of retinopathy was 33%.There was no significant difference between bladder

dysfunction group and group which did not have bladder dysfunction (P=0.226). Bladder dysfunction was seen 22 patients without retinopathy.

In a small study on 17 insulin dependent diabetic patients with median age of 45 years (27-67years) and mean diabetes duration of 23 years (14-44years) who suffered from diabetic nephropathy, no association was found between diabetic cystopathy and progression of nephropathy [10]. The frequency of nephropathy was 19% among patients with diabetic cystopathy in the study by Frimodt-Moller [80]. Serum creatinine was highly significant among those with nephropathy and cystopathy (P<0.001). In our study serum creatinine was significantly different in bladder dysfunction group and those who did not have bladder dysfunction. However there was no significant correlation between bladder dysfunction and nephropathy. There were two patients with renal failure in the bladder dysfunction group, whose altered renal function is probably because of diabetic nephropathy rather than cystopathy as both had macroalbuminuria.

As denoted by Kaplan et al [35], classical diabetic cystopathy was not the common abnormality seen among diabetic subjects; we found a variety of urodynamic abnormalities as denoted in the table 6. The present study was one to evaluate the prevalence of bladder dysfunction of probably asymptomatic diabetic subjects who had never come to urology department owing to their lower urinary tract symptoms and were recruited from a diabetic clinic of an endocrinology department.

Although most of the patients in our study were urologically asymptomatic or had mild symptoms as evidenced by the low mean IPSS, majority (35/45) of those

who had urodynamic evaluation had atleast one urodynamic abnormality. 7 (15.5%) had overt diabetic cystopathy and they never bothered to the extent of seeking urological advise. It indicates the very innocuous and occult nature of development of bladder dysfunction in diabetics. Unless they were questioned appropriately and diagnosed, they would have developed the classical cystopathy and its complications.

It's also worrisome to anticipate such complications happening in the group who did not have urodynamic evaluation. However considering ethical reasons, invasive urodynamic evaluation was not done in them. If we are able to predict the bladder dysfunction consistently using the uroflowmetry, post void residue and IPSS, it can be applied for screening the asymptomatic subjects. If any abnormality is detected during initial screening, they can be subjected to further urodynamic study, which is a more sensitive and accurate method of evaluating voiding function. The findings in this study suggest the development of diabetic bladder dysfunction begins far before symptoms appear or when symptoms are mild in nature. It highlights the importance of early screening for bladder dysfunction, especially for those who are at risk.

CONCLUSIONS

From this study, it can be concluded that

1) The prevalence of bladder dysfunction in diabetic subjects between 18 to 60 years of age from Tamilnadu attending a diabetic clinic was 41.1%.
2) Abnormal urodynamic findings other than diabetic cystopathy are commonly seen among the diabetic subjects.
3) IPSS, Uroflowmetry and estimation of post void residual urine might be useful to screen the diabetic subjects before urodynamic evaluation to diagnose and characterize bladder dysfunction.
4) Bladder dysfunction is seen often (35/45) in patients with moderate LUTS than in asymptomatic patients (2/45) or those with mild LUTS.
5) Bladder dysfunction is significantly associated with peripheral neuropathy and association with other microvascular complications like retinopathy and nephropathy is not significant.

LIMITATIONS

1) Small sample size of one particular community (Tamil speaking local people) may not represent the whole of the population of diabetic subjects in the country. Regional difference among various subjects and its implication on bladder dysfunction is not addressed. Larger sample size involving participation of subjects from varied geographical distribution might be useful to overcome the regional bias.
2) To elucidate the prediction of the chance of developing bladder dysfunction by the parameters studied may give erroneous value, particularly in the small present population of diabetic subjects.
3) We have only evaluated for peripheral somatic neuropathy (in the extremities) and the presence of autonomic neuropathy was not evaluated.
4) Some of the abnormal findings may normally occur with aging. However, because of ethical issues in performing invasive urodynamic studies on asymptomatic or mildly symptomatic patients, there was no real representation of bladder findings from the asymptomatic group even though calculation of bladder voiding efficiency was used to predict voiding dysfunction in them. Urodynamic evaluation in these subjects can throw light on the true prevalence of asymptomatic bladder dysfunction and can be detected at a very early stage.
5) The lack of associations between some of the parameters evaluated in this study might be due to the relatively small sample size and the

consequent low power of the study. Studies with larger sample sizes can be performed in future to more accurately predict the bladder dysfunction. It should be possible to exactly predict the chances of bladder dysfunction using mathematical models with application of simple and clinically applicable measurements like uroflowmetry, post void residue and IPSS.

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ANNEXURE

Proforma

Name: Age/Sex:

Hospital No: Address for communication:

Associated diseases**:**

Date of diagnosis of diabetes:

History:

1) Duration of Diabetes:

2) Lower urinary tract symptoms (LUTS):

3) Duration of LUTS:

4) Other urological symptoms

a) Hematuria, Calculuria, Chyluria, Necroturia yes / no

b) UTI / Instrumentation: yes / no

c) Previous voiding dysfunction: yes / no

5) Neurological, cardiovascular and peripheral vascular diseases.

6) Angina / Claudication / TIA: yes / no

Tools for evaluation:

1) International Prostate symptoms score:

2) Bladder diary for 24 hours:

3) Uroflowmetry and post void residual urine:

Examination:

Height: Weight: BMI:

Pulse: BP:

Distal pulses/ Reflexes:

Upperlimb:

Lower limb:

Peripheral sensation: Vibration / Pinprick

Biothesiometer:

Monofilament:

Fundoscopy:

Dry skin/ Hair loss / Deformities:

P/A: Bladder distension and other masses.

DRE: Sphincter tone, BCR, Prostate size.

External Genitalia:

Perineal sensation:

Spine:

Investigations:

1) Serum creatinine 2) AC/PC

3) HbA1C 4) Lipid profile

5) Micro albumin/mg/g of creatinine or 24 hr protein. 6) Urine Microscopy

7) Urine culture and sensitivity

8) X-ray KUB and Ultrasonography (when clinically indicated)

9) Urodynamic Parameters when applicable

Diagnosis:

Consent:

I, Mr / Mrs / Miss……., have been recruited to be a participant of this study. I was explained by the doctor undersigned that this study is intended to know occult bladder dysfunction in diabetic patients like me. I know that this condition doesn't manifest early and when if manifests, it is usually associated with multiple complications. I know that this study involves invasive procedures like urethral and rectal catheterization followed by urodynamic evaluation. I was informed of the possible complications involved in this study. I am aware that the results of this study may or may not have bearing on my treatment. I give consent for the proposed study after knowing all the benefits and complications.

Dr.R.Shanmugasundaram …….

Date Name of the patient

Name	Age	Sex	H.No.	TOD	DOD	IPSS	UF	VV	PVR	Ht.	Wt.	PR	BP	BMI	M
Kamala	57	f	038203b	2	14	12	33	610	23	146	56	80	140/80	26.3	4
Varalakshmi	51	f	907904c	2	1½	9	30	541	176	155	63	80	120/80	26.2	>
Gracy Albert	40	f	100605D	2	8	9	36	502	69	160	58	84	130/80	22.7	2
Sundaram	43	m	102734d	2	1	9	23	934	20	157	46	84	120/80	18.7	2
T.S.Saroja	55	f	947944b	2	20	10	16	489	5	159	78	78	140/70	30.9	2
Lakshmi	54	f	057182d	2	1	9	36	267	10	156	87	72	150/90	38.7	2
chandran	55	m	368956a	2	7	9	9	210	10	167	75	76	110/70	26.9	2
Annamalai	46	m	825817b	2	1	9	15	315	5	164	57	68	140/80	21.2	2
Vincent	37	m	071003c	1	6	0	9	580	130	174	55	78	110/70	17.5	2
Gangadharan	43	m	248163c	1	5	16	10	205	10	157	55	80	100/90	22	6
Manoharan	45	m	701260a	1	25	1	30	670	63	164	72	86	130/90	26.8	4
Natarajan	51	m	991144c	2	6	21	12	603	21	184	75	82	130/80	22.2	2
Balaraman	50	m	823096c	2	1	0	9	352	191	167	53	76	130/90	19	1
Jeyaprakash	54	m	229293c	2	1	9	14	465	47	168	59	82	110/70	20.9	2
Parasuraman	51	m	928071c	2	1½	9	22	600	13	165	65	72	120/80	23	1
Gnanasekar	39	m	338946c	2	6	15	15	347	75	168	71	76	120/80	24	2
Vijayakumar	57	m	756053c	2	13	23	9	159	210	165	69	78	160/80	25.3	4
Naushadh	46	m	112049D	2	1	9	12	169	19	167	71	60	126/70	25.5	2
P.R.Harinath	20	m	085619c	1	7	12	25	447	7	157	45	110	130/80	18.3	2
Kesavan	53	m	955002b	2	12	12	21.5	260	61	180	90	76	120/80	27.8	6
Balu	52	m	919615c	2	3	11	24	232	5	170	55	86	80/60	19	6
Mohanraj.T.E	55	M	110355D	2	7	9	20	252	7	158	80	82	170/100	32	2
Rani	44	f	444743c	2	4	9	14	164	26	159	60	68	138/84	23.7	2
Naushadh	46	m	112049d	2	1	9	12	269	19	167	71	60	126/70	25.5	2
Subramaniam	58	m	081887D	2	10	8	12	264	10	164	86	84	140/80	31.8	4
Susai	50	m	818668c	2	3	4	15	475	210	168	57	90	110/70	20.2	1
Janakiraman	57	m	253960a	2	18	28	6	341	75	160	62	80	140/90	24.2	4
Madhavi	43	f	700631a	2	9	10	36	466	45	153	72	72	110/70	30.8	2
Jeganathan.S	48	m	320660c	2	6	11	7.3	247	5	170	70	76	150/80	24.2	4
Syed Moosa	50	m	492867a	2	22	7	9	24	210	162	67	76	140/80	25.5	1
Antony Raj	51	m	259866c	2	11	12	26	384	88	164	66	82	120/80	24.5	4
Sumathy	34	f	640171c	2	2	12	38	524	22	151	51	64	120/80	22.4	2
Ilakkuvan	56	m	155088d	2	10	13	8	353	7	158	55	80	130/80	23.2	2
Mahendiran	44	m	272348B	2	10	14	12	202	37	177	95	76	110/70	30.3	2
Banumathi.S	50	f	833204c	2	2	8	21	296	10	160	59	70	130/80	23	2
Anusuiya.S	47	f	802119c	2	11	9	24.2	620	36	158	68	88	180/90	27.2	>
Somasundaram	50	m	106743d	2	3	7	8	505	60	155	54	86	110/70	22.4	>
Rajenderan. P	53	m	146250d	2	10	9	10	300	10	163	60	80	130/80	22.6	2
Ramalingam	49	m	080338d	2	15	11	15	524	9	162	56	72	120/80	21.3	2
sundaramurthy	56	m	243325c	2	15	3	10.8	238	26	157	48	76	140/80	19.5	2
Rajagopal.K	38	m	464150c	2	2	4	12	263	7	151	58	85	120/80	25	2
Puniyakodi	39	m	983115c	2	9 m	8	32	294	5	167	74	55	130/80	26.5	2
Nasuruddin	52	m	278183b	2	12	11	13	522	9	172	62	72	110/70	21	4
Neelavathi	46	f	109842a	2	3	15	24	338	42	156	83	84	120/80	34.1	2
Seethamma	36	f	190987c	2	1	9	49	628	36	151	70	70	130/80	30.7	6
Vijayan	29	m	284941c	1	4	3	19	432	14	163	49	88	120/70	18.6	2
Lakshmi	24	f	882372c	1	11	4	33	858	5	151	45	72	110/70	19.7	2
puroshothaman	44	m	441505c	2	5	2	18	726	48	167	73	76	110/70	26.2	2
Deivayanai	34	f	812741c	2	2	1	29	202	5	145	57	78	110/70	27.1	2
Krishnamoorthy	50	m	030608b	2	9	2	28	957	25	162	71	80	140/90	27.1	2
Rose mary	50	f	966064c	2	3	3	30	301	15	152	45	80	140/80	19	2

Banumathi	47	f	099419d	2	2	4	30	386	15	149	71	80	120/80	32	2
Lakshmi	44	f	003651a	2	1	2	20	270	5	158	63	84	120/70	25.2	6
John Abraham	40	m	421149a	2	5	3	25	610	14	165	63	72	120/80	23.1	2
Vijayakumar.S.K	43	m	045174d	2	6	4	15	214	10	164	67	90	140/90	24.3	4
Rani	47	f	084177d	2	8	2	26	538	20	154	71	76	110/80	29	2
Haridoss	49	m	999333c	2	6 m	0	25	412	25	160	72	80	130/80	28.1	2
Palani.A.D	37	M	122855C	2	2	2	24	175	8	170	69	76	120/80	23.9	2
Raghunathan	46	m	061986d	2	1	2	20	371	10	168	69	80	130/80	24.4	2
Gnanasekaran	53	m	076404d	2	10	4	16	393	4	185	81	80	120/80	23.7	2
Shanmugam.S	31	m	021932d	2	6 m	2	32	228	5	165	59	78	120/80	21.5	2
Pappa	49	f	071788d	2	15	3	18	175	5	157	53	90	130/80	21	1
Annakili	39	f	097847d	2	2	6	44	489	25	159	70	88	140/80	27.7	2
Suresh Babu	47	m	546892b	2	6	2	20	842	123	161	61	88	150/90	23.5	2
Radhakrishnan.S.V	55	M	767973C	2	20	5	20	309	8	160	68	82	130/90	26.6	2
Sumathi Rani	36	f	287033c	2	2	0	29	784	49	168	91	84	140/80	32.2	2
Vinod Chander	32	m	846405c	2	2	2	15	251	5	167	80	96	100/60	28.7	4
Sundaram	51	m	303287b	2	2	7	19	623	58	170	74	84	120/80	25.6	2
R.K.Venkatesan	34	m	626174c	2	1	7	18	154	10	172	78	82	132/80	25	2
Parimala	48	f	027551d	2	10	4	19	331	14	146	45	72	110/70	21.1	2
Anandan.S	42	m	759110c	2	2	2	39	696	51	177	82	76	120/80	26.2	2
Lakshmi	52	f	637313	2	7	2	47	512	5	151	71	80	140/80	31.1	4
Krishnaswamy.R	40	m	637641c	2	1	5	20.7	293	5	168	70	86	140/90	24.8	2
Elumalai	33	m	132488c	2	1	0	20	311	99	169	66	84	130/80	23	2
Sakthivel	55	m	449877	2	25	1	19	350	5	170	65	80	120/80	22.5	2
Geetha.S	47	f	127656d	2	12	6	24	360	5	160	55	86	130/80	21.5	2
Govindaraj.M	54	m	070583d	2	10	7	23	512	93	166	49	78	126/80	17.8	1
Chandru	42	m	650044c	2	4	2	20.6	745	52	162	57	84	120/70	21.7	4
Annadurai	46	m	941395c	2	6	1	23	129	4	161	62	78	140/80	23.9	4
Ishaar shariff	43	m	895984c	2	6m	1	20	207	5	169	113	88	150/90	39.6	2
Mohan.N.K	50	m	300227b	2	5	3	21	172	10	167	70	76	120/80	25.1	2
Subramani	53	m	074069d	2	1	6	31	416	19	165	50	80	130/80	17.9	2
Suresh kumar	40	m	478600	1	7	4	25	458	19	158	45	68	110/80	18	2
Baskar.S	42	m	978786c	2	8	6	36	534	38	170	67	80	114/80	23.2	2
Srinivasan G	41	m	754208b	2	8	3	25	533	114	174	80	72	140/80	26.4	2
Esther Shanthi	29	f	138495d	2	1½y	3	34	288	24	155	69	70	130/90	28.7	2
Sivakumar	50	m	438547a	2	15	0	31	545	37	175	75	88	110/80	24.5	2
M.R.Sriram	32	m	941508c	2	1½y	3	27	384	5	176	93	80	140/90	30	2
Arockiaswamy.B	57	m	437689c	2	3	1	18	213	10	175	53	64	110/80	18.3	2
Shanmugam.K	50	m	587254c	2	2½y	1	18	168	10	156	56	84	130/80	23	2

S. Cr.	AC	PC	HbA1C	Microalb	Chol.	TG	HDL	LDL	Ass. diseases	FS	MCC	Comp.	DI	IC
0.8	255	178	10.8	70	108	93	29	57	HT, hypothyroidism, depression	201	759	16	Nil	SI 51
0.6	155	196	8.6	488	249	262	46	151	Hypertension,Dyslipdemia	135	648	16	nil	nil
0.7	173	267	9.6	22	197	238	38	118	Dyslipidemia	152	764	9	Prt	UI
0.9	97	234	7.9	24	210	192	35	128		277	699	6	Nil	Ni
0.8	202	299	9.4	52	182	166	37	123	hypertension, IHD	162	674	10	Nil	Ni
1	144	235	8.2	42	162	95	32	120	hypertension	206	576	32	Prt	Ni
1.1	129	179	6.3	10	140	165	43	68	IHD	357	590	9	Nil	Ni
1	98	146	6	44	235	207	35	157		174	594	39	Nil	Ni
0.9	218	167	6.8	5	173	37	46	118		271	591	24	Nil	Ni
0.9	101	159	6.8	60	143	152	29	85	Asthma	337	522	20	Nil	Ni
1	111	100	6.6	22	126	82	41	73	athsma, PSVT, Hypertension, Dyslipidemia	337	717	11	Nil	Ni
0.8	171	276	8.9	8	235	200	44	136		179	805	4	Nil	Ni
1	93	138	5.7	27	140	254	29	78		327	717	38	Nil	Ni
0.8	143	173	10.6	63	138	72	29	102	chronic liver disease, Portal HTN,	312	618	27	Nil	Ni
0.9	106	247	7.1	33	97	225	28	45	Hypertension, IHD	219	726	12	Nil	Ni
1	150	219	8.4	22	144	233	28	78	hypertension	225	692	12	Nil	Ni
2.2	110	324	8.6	342	232	213	36	154	hypertension, IHD	321	670	20	Prt	Ni
1	158	238	8.6	150	192	208	40	117		205	438	10	Nil	Ni
0.8	134	288	12.5	150	154	82	37	104		155	695	12	Nil	Ni
0.8	186	322	10.9	220	178	126	38	112		336	887	8	Nil	Ni
1	212	287	13	38	228	187	36	150	cardiomyopathy	278	611	24	Prt	Ni
0.9	161	248	10.3	150	226	178	32	126	hypertension	188	520	7	Prt	UI
0.7	150	261	8.1	12	170	120	32	123	Asthma	178	461	15	nil	Ni
1	158	238	8.6	>150	192	208	40	117		205	438	10	nil	Ni

0.9	118	183	6.4	58	146	133	28	101	hypertension	307	664	16	nil	Nil	
0.8	84	151	7.6	9	163	124	31	113		244	656	10	Prt	Nil	
1	122	152	6.2	6	262	378	42	144	duodenal ulcer	169	299	19	Nil	Nil	
0.9	105	151	7.2	<5	149	85	38	95	hypertension	178	610	24	Nil	Nil	
1	124	293	8.6	24	149	98	28	95	post mitral valve repalcement	211	483	24	Prt	Nil	
1.3	108	168	10.5	113	269	108	50	202	ESRD- status post renal Tx	659	###	20	Nil	Nil	
1.1	61	148	7.4	104	150	173	36	80	Hypertesnion, dyslipidemia, IHD-POST CABG	178	428	7	Prt	Nil	
0.6	121	158	9.7	23	235	91	45	171		201	689	11	Nil	Nil	
1	220	417	10.9	<5	198	124	33	144	hyperstension	118	355	20	Prt	Nil	
0.9	112	138	6.6	<5	128	85	29	85	Panic disorder, IHD	134	271	16	Prt	UI	

0.7	115	150	7.6	20	173	191	36	103		214	648	10	Prt	Nil	
0.9	136	312	12.8	332	180	153	33	116	hypertension, diabetic foot	309	704	11	Prt	Nil	
1.2	69	210	10	6	134	91	32	77	Hypertension, dyslipidemia, IHD	184	311	24	Prt	UI	
1	312	411	9.3	23	176	136	30	110		209	519	24	Prt	UI	
0.8	122	283	9.2	56	262	256	50	174	hypertension, IHD, Effort angina, pul.TB	65	637	10	nil	Nil	
1.1	136	132	6.1	199	177	116	31	132	dyslipidemia	90	654	14	nil	Nil	
1	129	278	9	<5	135	305	31	67	dyslipidemia	278	832	18	nil	Nil	
0.9	140	200	6.5	24	172	114	32	113	cardiac arrhythmias	150	677	24	nil	Nil	
0.9	166	257	12.4	63	159	181	27	99	hypertension, IHD, LV dysfucntion	258	606	18	nil	Nil	
0.7	166	272	9.5	235	190	146	36	138	Hypertension	241	908	18	nil	Nil	
0.7	119	98	6.2	64	126	105	28	84	Hypertension	235	782	9	nil	Nil	
0.8	162	190	8.8	20	167	60	51	98	nil						
0.5	233	174	8.7	22	141	79	32	54							
0.9	170	218	7.9	<5	113	56	34	92	nil						
0.7	96	108	6.1	<5	162	159	31	99	nil						
1	149	203	7.4	26	181	164	32	142	Hypertension, dyslipidemia						
0.7	171	264	7.3	149	255	240	42	186	Dyslipidemia						
0.9	119	225	9.8	30	210	170	41	151	Hypertension, post menopausal						
0.8	88	130	5.7	<5	136	59	35	79	Dyslipidemia						
1.1	129	128	6.8	<5	153	100	39	88							
0.8	252	342	8.9	51	242	229	37	173	Dyslipidemia						
0.8	125	184	9.6	7	203	267	43	130							
1.2	137	274	6.1	>150	177	372	39	96	AK amputee, dyslipidemia						
1	93	120	6.3	15	165	84	29	121							
1	240	322	9.6	12	198	244	35	122							
1	170	267	10.8	29	152	93	31	110	hypertension, IHD-MI,dyslipidemia						
0.9	142	173	8.7	<5	153	92	31	84							
0.8	167	334	12.3	13	313	383	48	216	hypertension, dyslipidemia						
0.8	130	220	6.7	33	273	196	54	175	hypertension,dyslipidemia						
0.9	158	147	7.5	99	184	116	38	136							
0.9	118	177	7.6	24	220	187	38	153	dyslipidemia						
0.7	153	167	8.5	<5	162	125	41	104	hypertension, obesity						
1.2	147	252	8.8	<5	159	136	29	98							
0.9	83	104	6.6	15	154	60	44	90	post pneumonectomy-TB						
1	182	244	7.5	150	192	175	44	113	hypertension, dyslipidemia						
0.8	153	247	7.5	162	178	201	40	110	IHD, dyslipidemia						
0.9	103	128	5.7	<5	171	145	30	123	hypertension, dyslipidemia						
0.6	110	168	7.8	24	201	182	41	144	Dylipidemia, obesity						
1.1	106	215	6.4	7	212	152	42	151							
0.8	125	189	6.8	<5	218	286	40	121							
0.8	129	242	10	<5	131	79	25	88	IHD, dyslipidemia						
0.7	172	305	10.1	5	296	108	43	235	Dyslipidemia						
0.8	102	228	>13	48	119	79	29	57	Hypertension, pulmonary TB						
0.8	168	281	11.5	<5	210	138	40	150							
1	93	119	6.2	9	157	187	35	99	hypertension, dyslipidemia						

0.9	114	119	9.1	20	174	161	39	112	hypertension,metabolic syndrome
1	112	78	6.4	5	183	85	29	163	
0.9	101	225	6.2	38	171	132	36	122	dyslipidemia
1	144	295	12.2	16	162	87	30	109	Hypothyroidism
1	135	210	8.2	15	162	129	33	84	
1	107	140	6.5	<5	153	87	31	104	hypertension
0.9	148	351	8.5	14	166	203	40	104	
0.8	93	141	7.3	150	127	66	24	93	hypertension,IHD,dyslipidemia, bell's palsy
0.9	226	350	10.1	3	186	165	31	139	infertility,dyslipidemia
0.9	277	434	10.9	9	247	299	44	160	
0.9	177	270	7.8		172	132	35	122	